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RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP NO. 1631

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Ecker, Griffey, Crooke, Sampath, Swayze, Hofstadler, and McNeil**

Title: **Modulation Of Molecular Interaction Sites On RNA And Other Biomolecules**

Serial No.: **09/076,404**

Group Art Unit: **1631**

Filed: **May 12, 1998**

Examiner: **John S. Brusca**

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

RESPONSE UNDER 37 C.F.R. §1.116

In response to the Final Rejection dated November 17, 2008 in regard to the above-identified patent application, Applicants respectfully request that the rejections therein be reconsidered.

Claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 are pending in the present application.

As a preliminary matter, Applicants have filed herewith an electronic copy of USSN 09/076,447, which was listed in a previously filed Information Disclosure Statement.

I. The Claimed Invention Is Supported by Ample Written Description

Claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. The Office continues to assert that Applicants' specification "does not describe the structure of human target RNA sequences with an interaction site that is **less** than 30 nucleotides in length" (see, page 3 of the Final Rejection; emphasis in the Final Rejection). Applicants traverse the rejection and respectfully request reconsideration because the specification provides ample written description supporting the claims.

As a preliminary matter, Applicants are not generically claiming all RNA targets having a molecular interaction site less than 30 nucleotides. Rather, claim 19, for example, recites a method of identifying a compound that binds to a human target RNA. One step of such method recites that a three dimensional representation of a molecular interaction, less than 30 nucleotides, is generated *in silico*. The Office mistakenly asserts that Applicants are not in possession of molecular interaction sites of less than 30 nucleotides.

First, the Office is again reminded that Applicants' specification teaches:

> Applicants' invention is directed to methods of identifying secondary structures in eukaryotic and prokaryotic RNA molecules termed "molecular interaction sites." **Molecular interaction sites are** small, usually **less than 30 nucleotides**, independently folded, functional subdomains contained within a larger RNA molecule.

(see, page 15, line 30 to page 16, line 2 of the specification). Thus, this portion of the specification alone provides ample written description showing that Applicants were in possession of the claimed invention.

Second, Applicants' specification provides ample guidance and written description for identification and/or assembly of target RNA molecules and identification of conserved regions within these molecules (see, for example, pages 26-39). These conserved regions, if possessing secondary structure, are molecular interaction sites. Applicants' specification further teaches that when generating a series of sequences, a plurality of nucleic acids having at least a portion of their nucleotide sequences which are homologous to at least an 8 to 20 nucleotide region of the target nucleic acid results (see, for example, page 34, lines 20-22). Further, Applicants' teach that the "window size" for homology can be from about 8 to about 20, or from 10-15, or about 11-12 (see, for example, page 34, lines 26-28). Applicants also teach that a window from about 10 to about 30 nucleotides, as well as a window of 21 nucleotides can be used to identify conserved

sequence regions (see, for example, page 38, lines 7-17). Again, it is these conserved regions among RNA targets that contain molecular interaction sites. Once these conserved regions are identified, Applicants specification provides ample guidance and written description for determining whether the conserved regions have secondary structure (see, for example, pages 39-44). Thus, these portions of the specification also provide ample written description showing that Applicants were in possession of the claimed invention.

Third, Figures 40-44 of Applicants' specification relate to a 27-mer RNA target corresponding to the 16S rRNA A-site. This 27-mer is also discussed in Examples 13-16. In addition, Example 12 discusses a 5'-UTR containing a 27-mer RNA construct of the HIV TAR stem-loop bulge. These 27-mers are examples of molecular interaction sites.

Thus, the specification as a whole provides ample written description of a molecular interaction site having "less than 30 nucleotides."

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly failing to provide sufficient written description be withdrawn.

II. The Claimed Invention Is Not Obvious

Claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of the following references: 1) Murray et al., J. Computer-Aided Mol. Des., 1997, 11, 193-207 (hereinafter, the "Murray reference"), 2) U.S. Patent No. 6,337,183 (hereinafter, the "Arenas reference"), 3) Sezerman et al., Protein Sci., 1993, 2, 1827-1843 (hereinafter, the "Sezerman reference"), 4) Greig et al., J. Am. Chem. Soc., 1995, 117, 10765-10766 (hereinafter, the "Greig reference"), and 5) Hentze et al., Science, 1987, 238, 1570-1573 (hereinafter, the "Hentze reference"). The Action asserts:

> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the screening method of Murray et al. by use of the RNA targets of Arenas et al. because Arenas et al. shows bioassays that screen for compounds that bind to RNA targets. It would have been further obvious to use mass spectroscopy to analyze binding strength because Sezerman shows that peptides may be analyzed in silico for binding, and Greig et al. shows that mass spectroscopy may be used to determine the binding affinity of a complex of a peptide and an oligonucleotide, and experimental determination of binding strength is an

> important parameter for determination of biological activity. It would have been further obvious to use the IRE target sequence of Hentze et al. because Hentze et al. shows that the human IRE RNA target sequence has a role in cell iron metabolism, and further can be used to confer regulation of translation on a mRNA of choice. Development of compounds that bind to the human IRE would allow for development of compounds that inhibit or enhance expression of wild type or recombinant genes in human cells as suggested by Arenas to allow for insights into the function of naturally occurring mRNA or to regulate gene expression of recombinant genes comprising the IRE.

(See, Final Rejection at pages 6-7). Applicants traverse the rejection and respectfully request reconsideration because combination of the cited references fails to produce the claimed invention.

It cannot fairly be said that the combination of cited references, which does not so much as mention some features recited in the claimed methods, render such methods obvious. Thus, rejection under §103 is improper since a case of *prima facie* obviousness cannot be made. *In re Payne*, 203 USPQ 245, 255 (CCPA 1979) (references relied upon to support rejection under §103 must place the claimed invention in the possession of the public). For example, claim 26 recites, in relevant part: "identifying *in silico* at least one molecular interaction site less than 30 nucleotides in length on said human target RNA **by comparing the nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species, identifying at least one conserved region, and determining the secondary structure of said conserved region**" (emphasis added). Applicants' undersigned representative has not been able to locate any portion of the cited references which teach these features.

The Office asserts that:

> Hentze et al. compares the human sequence to orthologous sequences from other species in figure 2 and the discussion on page 1572 and concludes that the sequence is highly conserved during evolution.

(See, page 6 of the Final Rejection). The Hentze reference, however, does not teach or suggest identifying *in silico* at least one molecular interaction site less than 30 nucleotides in length on said human target RNA **by comparing the nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species, identifying at least one conserved region, and determining the secondary structure of said conserved**

region" (emphasis added). Rather, the Hentze reference identified the IRE by constructing a series of deletion mutants and examining for the presence of iron responsiveness. The IRE was, in fact, identified by adding back a fragment to an iron-nonresponsive construct and looking for the rescue of iron responsiveness (see, entire Hentze reference). The portion of the Hentze reference relied upon in the Final Rejection does not support the assertion that the molecular interaction site was identified by "comparing the nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species, identifying at least one conserved region, and determining the secondary structure of said conserved region." Rather, the portion of the Hentze reference actually reports:

> Comparison of the core region of the human ferritin H-chain cDNA leader sequence (which contains the IRE) with the leader sequences of the human ferritin L-chain (15) and the cDNA sequences of ferritins from other species (16, 17), reveals that the core region of the predicted stem-loop structure has been highly conserved during evolution. This sequence predates the evolutionary segregation between amphibians, birds, and man which occurred more than 300 millions years ago (17).

(See, page 1572, middle column of the Hentze reference). This portion of the Hentze reference certainly does not support the allegation that the molecular interaction site was identified by "comparing the nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species, identifying at least one conserved region, and determining the secondary structure of said conserved region." Thus, even if the cited references are combined in the manner suggested by the Office, the invention recited in claim 26, as well as claims dependent thereon (i.e., claims 30, 40, and 41), is not produced.

The Office also fails to make out a *prima facie* case of obviousness in regard to the remaining independent claims. When making a *prima facie* case of obviousness, it remains necessary to identify some reason that would have led a person skilled in the art to modify the teachings of a reference in a particular manner. *Takeda Chemical Industries, Ltd. v Alphapharm Pty. Ltd.*, 492 F.3d 1350, 83 USPQ.2d 1169 (Fed. Cir. 2007). No such reasoning has been provided. The Office also asserts that "It would have been further obvious to use mass spectroscopy to analyze binding strength because Sezerman shows that peptides may be analyzed in silico for binding, and Greig et al. shows that mass spectroscopy may be used to determine the binding affinity of a complex of a peptide and an oligonucleotide…" (see, Final Rejection at

pages 6-7). The Sezerman reference reports computational determination of peptide-receptor structure using a docking computer program whereby conformationally flexible ligands are docked to a receptor. Interaction energy was calculated using CHARMm, which is a computer program. Thus, the Sezerman reference uses an entirely *in silico* method to dock ligands to a receptor and calculate the interaction energy of such docking. The Sezerman reference does not teach or even suggest replacing the CHARMm interaction energy calculating program with any other method of analyzing binding affinity, let alone an actual bench method, let alone mass spectrometry. Indeed, a goal of the Sezerman reference is to perform computational determination of peptide-receptor structure. Replacement of the CHARMm method of determining interaction energy between a peptide and a receptor with a mass spectrometric method of determining binding strength between an oligonucleotide and a serum albumin (as reported in the Greig reference) is nonsensical and defeats a goal of the Sezerman reference, i.e., a computational method of peptide-receptor structure. It is only upon examination of Applicants' specification that such claimed methods can be rendered obvious. Applicants respectfully point out that "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ.2d 1780, 1784 (Fed. Cir. 1992).

In addition, if a proposal for modifying the prior art in an effort to attain the claimed invention causes the art to become inoperable or destroys its intended function, then the requisite motivation to make the modification would not have existed. *See In re Fritch*, 972 F.2d at 1265 n.12 ("A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose."); *In re Ratti*, 270 F.2d 810, 813 (CCPA 1959) (holding the suggested combination of references improper under §103 because it "would require a substantial reconstruction and redesign of the elements shown in [a prior art reference] as well as a change in the basic principles under which [that reference's] construction was designed to operate"). In this regard, the Murray reference reports an *in silico* method of identifying virtual compounds that can bind to a particular site within a molecule. The Murray reference reports identification of thrombin inhibitors by a completely *in silico* method, in contrast to actually carrying out physical binding assays. Thus, a major goal of the Murray reference is to provide an *in silico* method, rather than actual physical methods, of

predicting binding of a potential therapeutic compound to a particular receptor. Any modification of the Murray reference that would add another layer of a completely different, let alone physical, technology such as mass spectrometry, would be counter to the *in silico* methodology of the Murray reference. Therefore, the requisite motivation to further modify the methodology of the Murray reference does not exist. In this regard, each of claims 19 (and dependent claims 20, 37, and 38), 32 (and dependent claims 33, 43, and 44), and 34 (and dependent claims 35, 46, and 47) recite "testing said highly ranked members to determine their ability to interact with said molecular interaction site by: contacting the human target RNA with at least one of said highly ranked members to provide a complex between the human target RNA and the member or members; ionizing said complex; fragmenting the ionized complex; and determining whether highly ranked members bind to the molecular interaction site of said human target RNA" or something similar thereto, and therefore are not obvious over the combination of cited references.

The Office responds by asserting that "the in silico and experimental approaches of these two references [the Murray and Greig references] are not in conflict, the two references show complementary methods of studying formation of binding complexes, each with advantages such as speed and ability to assay a large range of potential compounds for the in silico method, and accuracy and experimental confirmation of predicted complex formation for the mass spectrometry method" (see, Final Rejection at page 7). These observations by the Office, however, do not address the issue raised by Applicants. Indeed, the Office's proposal to modify the methodology of the Murray reference in an effort to attain the claimed invention destroys one intended function and requires a substantial reconstruction and redesign of the elements shown in the Murray reference as well as a change in the basic principles under which construction was designed to operate, i.e., in an *in silico* environment.

In view of the foregoing, Applicants claimed invention is not obvious in view of the picking and choosing and subsequent recombination of portions of five references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

III. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Office is invited to contact

Applicants' undersigned representative at 610.640.7859 if there are any questions regarding Applicants' claimed invention.

The Commissioner is hereby authorized to debit any underpayment of fee due or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

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Date: **14 January 2009**

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